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An Historical Overview: The Discovery of How NK Cells Can Kill Enemies, Recruit Defense Troops, and More

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Natural killer (NK) cells were originally defined as effector lymphocytes of innate immunity characterized by the unique ability of killing tumor and virally infected cells without any prior priming and expansion of specific clones. The "missing-self" theory, proposed by Klas Karre, the seminal discovery of the first prototypic HLA class I-specific inhibitory receptors, and, later, of the Natural Cytotoxicity Receptors (NCRs) by Alessandro Moretta, provided the bases to understand the puzzling behavior of NK cells. Actually, those discoveries proved crucial also for many of the achievements that, along the years, have contributed to the modern view of these cells. Indeed, NK cells, besides killing susceptible targets, are now known to functionally interact with different immune cells, sense pathogens using TLR, adapt their responses to the local environment, and, even, mount a sort of immunological memory. In this review, we will specifically focus on the main activating NK receptors and on their crucial role in the ever-increasing number of functions assigned to NK cells and other innate lymphoid cells (ILCs).

Keywords: human natural killer cells, innate immunity, natural cytotoxicity receptors, Toll-like receptors, activating NK receptors

INTRODUCTION

When Alessandro Moretta was appointed as Professor of Histology at the University of Genoa and started to set up a new lab and recruit people, including most of the authors of this review, the knowledge of how NK cells could exert their activity against tumors and viruses was very limited. The "missing-self" hypothesis had just been proposed by Karre and Ljunggren (1), but there was no idea on the molecular mechanisms by which NK cells could spare the "good" cells and kill the "bad" ones. Within <10 years, Moretta's lab generated a large number of monoclonal antibodies (mAbs) that allowed the identification and characterization of many key receptors, including,

among many others, the first-discovered Killer Ig-like receptors (KIRs) (2–4) and the Natural Cytotoxicity Receptors (NCRs) (5). These discoveries provided the mechanistic explanation of the "missing-self" theory. Indeed, they showed that NK cells could kill target cells by integrating signals from activating and inhibitory receptors, by recognizing ligands on tumor or virus-infected cells and by sensing changes in HLA class I expression (6–9).

Later studies indicated that NK cells, besides "killing the enemies," could also "incite the defense troops" by interacting with Dendritic Cells (DCs) to induce and polarize the adaptive immune response (10–12). A relevant role for given NK receptors newly identified by the Moretta's group, together with certain Toll-like receptors (TLRs), was found also in this context (13–16). This field was then further investigated, revealing the quite large net of interactions that NK cells can undertake with innate (granulocytes and macrophages) and adaptive immune cells, and even stromal and tumor cells (17–24).

After this early era of major discoveries, studies on NK cells increased exponentially, revealing an extraordinarily complex world, which now comprises a number of circulating or specialized tissue-resident NK cell subsets (25). Some studies also showed that NK cells can adapt their function to environmental changes or even maintain memory of certain viral infections (26–30). Moreover, many of the ligands for the activating NK receptors have now been identified and demonstrated to be variably expressed by tumor or virus-infected cells (31, 32). Much information have been added to the mechanisms that regulate the availability and function of NK cells within tumor tissues giving hints on the possible use of NK cells in the therapy of solid tumors (33–38). Finally, the extensive studies of the KIR repertoire and the "old" data on NK/DC interaction have posed the basis for a reliable exploitation of NK cells in hematopoietic stem cell transplantation (HSCT) to cure hematologic malignancies (39–42), while the new findings on the immune checkpoints regulating T and NK cell functions have reinforced the idea of blocking HLA class I-specific NK receptors to unleash the NK cell anti-tumor potential. In this context, human/humanized anti-KIR or anti-NKG2A mAbs or combinations of mAbs blocking NKG2A and the PD-1/PD-L axis are tested in animal models and clinics (33, 43–48).

Alessandro Moretta, who has continued his work on NK cells with immutable enthusiasm all over his life, also contributed to these latter advances in the field with many key data, spanning from the tumor escape mechanisms acting on the activating receptor expression, to the characterization of the memory-like NK cell subset, the role of activating KIRs, and the role of immune checkpoints on NK cells in tumor patients. Nevertheless, it is indubitable that the identification of the first KIRs (which will be treated in a review aside) and of many NK activating receptors represents his real landmark discovery and legacy to Science. Indeed, the characterization of these receptors impressed an acceleration of the initial research and, still now, represents the basis for many new findings on NK cells and beyond (**Figure 1**).

The association of different NCR splice variants with tumor tissues or with non-pathological decidua tissues, the role of NKp30, NKp46, and NKp80 in the NK-mediated cross-talk with DCs, granulocytes, or monocytes, and the definition of NKp46 and NKp44 as markers of non-cytotoxic ILCs, are only some of the indications for the involvement of these receptors in near future studies on NK cell-based therapies against cancer, for long-standing investigations on the maternal-fetal tolerance, and, more extensively, on tissue homeostasis.

NATURAL CYTOTOXICITY RECEPTORS

Only few years after the identification of the first KIRs and of CD94/NKG2A, three non-HLA class I-specific activating receptors (namely NKp46, NKp30, and NKp44) were discovered in Alessandro Moretta's lab. These receptors, together with NKG2D, turned to be crucial for the recognition of both tumor and virus-infected cells (5, 49, 50). They were first characterized for their functional features (i.e., their ability to induce NK cell cytolytic activity and cytokine release) (51–54) and then also at the molecular level, when the cDNAs coding for these receptors were isolated (53, 55, 56) and the crystallographic structures were solved (57–60). NKp46, NKp30, and NKp44 were all selectively expressed on NK cells (although their expression was differently induced during activation) and revealed, since the initial studies, to be the main receptors responsible for the so-called "natural cytotoxicity" of NK cells. Thus, based on these findings, these receptors were collectively termed as Natural Cytotoxicity Receptors (NCRs), although neither the protein structure, nor the gene location gave indications for their belonging to a receptor family. Their discovery paved the way to a huge number of studies aimed at elucidating their function in both physiological and pathological conditions and characterizing the NCR/NCR ligand (NCR-L) interactions. As mentioned above, NCR expression was initially thought to be confined to NK cells, and NKp46 is still being considered a reliable NK cell-associated marker, both in humans and in mice (61, 62). Soon thereafter it became clear that these receptors could also be expressed in other immune cell types (63), extending their role to additional biological processes. For example, the characterization of the heterogeneous family of Innate Lymphoid Cells (ILCs) (25, 64, 65) revealed that NKp44 is also expressed by IFN-γ-producing intraepithelial ILC1 and by a subset of ILC3 present at the epithelial/mucosal surfaces, in tonsils, and in decidua tissue (66–71). Notably, NKp44^{pos} ILC3 display a unique cytokine pattern, being able to produce IL-22 following cytokine stimulation (68). In these cells, NKp44 triggering induces TNF-α production and activates a pro-inflammatory program (72), suggesting that NKp44 could play a role in the pathogenesis of different immune-mediated disease, including psoriasis (73). In addition, NCR^{pos} (NKp44^{pos}) ILC3 have also been detected in the lymphoid infiltrate of non-small cell lung cancer, and have been found to release pro-inflammatory cytokines following interaction with tumor cells and tumor-associated fibroblasts (34, 67, 74). NKp46 expression has been detected in CD4^{pos} T lymphocytes derived from patients with Sézary syndrome, an aggressive form of cutaneous T-cell lymphoma (CTCL) (75). Notably, in these cells, NKp46 can act as an inhibitory co-receptor able to decrease CD3-mediated proliferation of Sézary

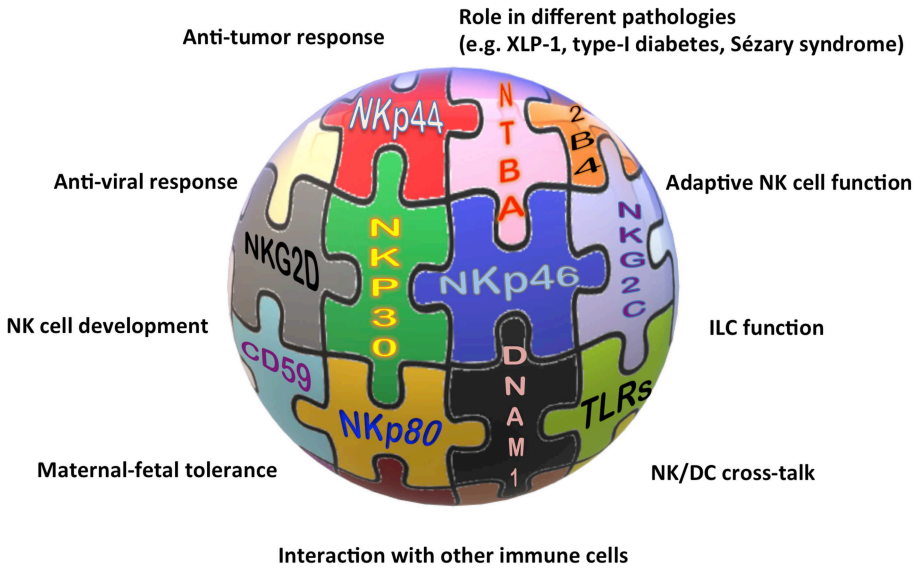

FIGURE 1 | The "activating" solution of the NK cell puzzle. Different activating receptors collaborate to induce NK cell triggering in healthy and pathological conditions.

cells, and has been proposed as an additional diagnostic marker, besides KIR3DL2, for the detection of these malignant cells (76).

One of the most investigated issues about NCRs is the characterization of their ligands. Although the landscape of NCR ligands is still incomplete, a common emerging theme is the multiplicity and heterogeneity of NCR/NCR-L interactions (31, 77–80). Most NCR ligands have been shown to activate NK cell function, while others dampen NK cell activation or act as "decoy ligands" when released in soluble form (81–85). The panel of cellular NCR-Ls currently includes surface glycoproteins, nuclear proteins that can be displayed at the cell surface, soluble molecules that can be either secreted, enzymatically shed, or conveyed through extracellular vesicles (82, 85–92). The expanding knowledge of NCR-Ls has opened the possibility of targeting NCR/NCR-L interactions in the context of cancer immunotherapy strategies. In addition, it has allowed the identification of several mechanisms of tumor escape related to the interaction between NK cells and malignant cells in the tumor microenvironment (22, 93–101). Finally, the importance of NK cell activity, and of NCRs in particular, in the therapeutic effect and outcome of oncolytic virotherapy has now being appreciated (102–104). NCR-Ls are also being studied as possible biomarkers in a variety of pathological conditions. Thus, a soluble form of B7-H6 (sB7-H6), an NKp30 ligand, has been demonstrated in the peritoneal fluid of ovarian cancer patients and in patients with metastatic gastrointestinal stromal tumor (GIST), neuroblastoma, or hepatocellular carcinoma (HCC) (83, 84, 105, 106). The presence of soluble BAG6/BAT3 (another NKp30-L) in the plasma of chronic lymphocytic leukemia patients was found to correlate with advanced disease stages (81). Along this line, high levels of soluble Nidogen-1, an NKp44 ligand, have been detected in the sera of patients with ovarian or lung cancer (107, 108).

Regarding the possibility of exploiting NCRs in anti-tumor approaches, it must be considered that NKp46 and NKp30 expression is down-regulated in NK cells derived from patients with different types of both hematological and non-hematological cancers (93, 109–116). This downmodulation leads to the impairment of NK cell anti-tumor potential and consequently to the need to develop strategies aimed at restoring NCR function (i.e., the use of cytokines, immunomodulatory drugs, anti-cancer drugs, or anti-KIR mAbs) (117–120). In addition, tumor cells themselves can become more resistant to NK cell-mediated attack by down-regulating NCR-Ls or releasing them in a soluble form (decoy ligands).

The role of NCRs stretches beyond cancer. B7-H6 is also involved in the inflammatory response: its expression is induced on monocytes following exposure to pro-inflammatory cytokines or TLR ligands, and high levels of sB7-H6 are found in the serum of patients with sepsis induced by Gram-negative bacteria (121). NK cells, in general, have been studied in different autoimmune disorders, including systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and type I diabetes (TID) (122–124). Focusing on NCRs, NKp46 has been shown to play a role in the pathogenesis of TID and in the destruction of normal pancreatic β cells (125), suggesting the possibility to target this receptor through specific anti-NKp46 mAbs (126).

A few years after the NCR discovery, the existence of different splice variants of these receptors was revealed (32, 127). Thus, three alternatively spliced NKp30 isoforms were identified, characterized by distinct intracellular regions and different functional capabilities. In GIST patients the prevalence of NKp30c isoform has been associated to decreased NK cell functionality and to reduced survival (128). Along this line, a similar pattern of NKp30 isoform expression has been detected in HCC patients (106). Notably, NKp30c isoform and sB7-H6 have

been studied in metastatic GIST patients, revealing their possible use as predictive biomarkers of disease progression and response to imatinib mesylate treatment (105). NKp44 splice variants have been studied in different neoplastic disorders, and in particular in acute myeloid leukemia patients, indicating a correlation between the prevalence of the ITIM-bearing inhibitory NKp44-1 isoform and poor survival (129). The induction of NKp44-1 expression has been also observed in decidua NK cells, driven by cytokines released in the decidua microenvironment, and could play a role in promoting tolerance toward the fetus (127, 130).

Among the NCRs, NKp44 is the main receptor involved in the interplay between NK cells and trophoblast cells during pregnancy (131, 132), and is expressed also by a subset of ILC3 and by IFN-γ-producing ILC1-like cells found in the decidua (133). Decidua NK cells represent a peculiar NK cell subset, characterized by NKp44 expression, poor cytotoxic activity, and contributing to decidua development, vascularization, and tissue building/remodeling (134–136). Notably, in these cells, NKp44 triggering has been shown to induce IP10, IL-8, and VEGF release (132, 137).

ACTIVATING CO-RECEPTORS

Alessandro Moretta gave fundamental contributions also to the identification and/or characterization of other surface receptors, including 2B4 (138–140), NTBA (141, 142), CD59 (143), and NKp80 (144), that play a complementary or a synergistic role with NCRs in inducing NK cell activation. Some of these molecules received great interest because of their involvement in NK cell function and development. 2B4 (145, 146) and NTBA (142), belonging to the signaling lymphocyte activation molecule (SLAM) family, have been shown to act as co-receptors, able to potentiate NK cell cytotoxic activity induced by the main triggering receptors, including NKp46 (140, 141). While 2B4 receptor recognizes CD48 (146, 147), NTBA is involved in homophilic interactions (142). Notably, 2B4 and NTBA dysfunction was described to be associated with a severe form of immunodeficiency, the X-linked lymphoproliferative syndrome type 1 (XLP-1), caused by mutations in *SH2D1A*, the gene encoding the signaling lymphocyte activation molecule (SLAM)-associated protein (SAP) (148). Interestingly, in the absence of SAP, the 2B4 and NTB-A co-receptors associate with the protein tyrosine phosphatases thus delivering inhibitory, instead of activating, signals (141, 149–151). This immune dysfunction is mainly responsible for the NK cell inability to kill EBV-infected B cells (B-EBV) that express CD48, resulting in extremely severe clinical consequences. A rapid diagnostic flowchart for XLP1, based on a 2B4-specific functional assay, combined with intra-cytoplasmic SAP staining, has been proposed (152). Moreover, the abnormal 2B4 function also influences 2B4 cross-talk with other NK receptors. Indeed, inhibitory 2B4 molecule selectively blocks ITAM-dependent activating receptors, namely NCR and CD16, while it affects neither NKG2D nor DNAM-1, which do not transduce through ITAM (152). This finding explains the selective inability, shown by NK cells, to kill B-EBV cells, which highly express CD48 and are mainly recognized by NCRs. In addition, in the NK cell repertoire of XLP-1 patients, NK cells lacking any self HLA class I-specific inhibitory receptor are highly represented and fully functional, indicating that the inhibitory 2B4 participates to NK cell education (153). Interestingly, a similar role for 2B4 has been described also in particular non-pathological processes. Indeed, at early stages of NK cell differentiation, when HLA class I-specific inhibitory receptors are not yet expressed, the delivery of inhibitory signals by 2B4, as a consequence of the late SAP expression, renders self-tolerant immature NK cells that otherwise would be autoreactive (154). Another peculiar situation is represented by decidua NK cells, in which 2B4 functions as an inhibitory receptor due to the absence or very low levels of SAP expression (155).

CD59 has been found to associate to NKp46 and NKp30 receptors and to enhance NK cell-mediated cytotoxic activity (143).

NKp80 molecule was initially described as a co-receptor, expressed by all NK cells, and able to cooperate with triggering receptors in the induction of natural cytotoxicity (144). Later, NKp80 was found to recognize the Activation-Induced C-type Lectin (AICL), a myeloid-specific activating receptor expressed by monocytes, macrophages, and granulocytes (156). NKp80-AICL interaction results in the secretion of pro-inflammatory cytokines from both cell types. In addition, it has been shown to participate in the NK cell-mediated elimination of malignant myeloid cells (156). NKp80 also plays an important role in the process of NK cell development. Indeed, it marks functionally mature NK cells developing in secondary lymphoid tissues (SLT). In particular, on the basis of NKp80 expression, two distinct subsets of SLT stage 4 cells can be distinguished: an $NKp80^{neg}$ population with both NK- and ILC3-associated features and an $NKp80^{pos}$ population with features similar to PB $CD56^{bright}$ NK cells (157).

Among the surface molecules behaving as co-receptors in the activation of NK cell functions, a major role is assigned to DNAX Accessory Molecule (DNAM-1 or CD226), an adhesion molecule displaying activating function, expressed not only by all NK cells but also by T lymphocytes and monocytes (158). Alessandro Moretta's group gave an important contribution in this field with the identification of two different DNAM-1 ligands, namely PVR and Nectin-2, belonging to the Nectin family (159). These molecules are widely expressed on a variety of both hematological and solid tumors (160, 161), representing suitable targets for immunotherapeutic approaches (162). The role of DNAM-1 ligands in tumor cell recognition and killing by NK cells is actually more complex, since, besides DNAM-1, also the inhibitory receptors CD96 and TIGIT can recognize PVR or PVR and Nectin-2, respectively (163, 164). Accordingly, TIGIT and CD96 have been proposed as immune checkpoints, and are becoming appealing targets for the development of antibodies to be used in combination with other immune checkpoint inhibitors with the aim of unleashing both T and NK cell cytotoxic potential against tumors (165, 166).

ROLE OF NK CELLS IN IMMUNE REGULATION

NK-DC Crosstalk

In the late '90s, it was becoming evident that innate immune cells do not act in isolation but potentiate their efficiency by interacting with each other, resulting even in the regulation of adaptive immune response. In 2001 Ralph Steinman (eventually a Nobel Laureate for the discovery of dendritic cells) visited our laboratories in Genoa and that occasion represented a starting point for a fruitful collaboration aimed at investigating the cross-talk occurring between human DCs and NK cells. As always, Prof. Moretta's insights were pivotal in all the studies carried out in that period, identifying which receptors and which subsets of these two innate immune components participate in this interaction, how this last one influences immune responses and to which extent similar stimuli (e.g., TLR ligands) are integrated by DCs and NK cells during innate immunity.

Until then, DCs were known for their critical role in initiating immune responses and priming antigen-specific T cell response (167), acting as sentinels in peripheral tissues, continuously sampling the environment. The dogma also foresaw that upon activation by danger signals, they up-regulated chemokine receptors and co-stimulatory molecules, which allowed them to migrate into lymph nodes and to efficiently induce T cell responses (167). Thus, the idea that DCs could also act as early activators of innate lymphocytes and, in turn, receive activating signals by activated NK cells, was ground-breaking in the field of innate immunity (14).

One of the relevant outcomes of NK/DC interaction is the so called "editing" of DCs, a term coined by Prof. Moretta to indicate the ability of NK cells to eliminate DCs in immature stage, and therefore *bona fide* tolerogenic DCs, while sparing activated/mature DCs able to efficiently induce the subsequent adaptive immune response in secondary lymphoid organs (12, 168, 169). The protective mechanisms of mature DCs was identified in the up-regulation of HLA class I molecules, especially of the non-classical HLA-E (170), occurring upon activation of DCs by either danger signals or NK cells themselves. At the same time, also the activating receptors involved in DC recognition by NK cells were identified (12, 171). The relevance of NKp30 receptor in NK/DC cross-talk was not limited to the mechanisms of killing of immature DCs but extended to the maturation process of DCs upon interaction with NK cells (172).

Remarkably, this cytolytic DC editing by NK cells was identified as a NK-mediated capability of dampening the graft-vs.-host disease in bone marrow transplantation (40) and graft rejection in solid organ transplantation (173, 174). It is noteworthy that, in case of improved skin graft rejection, NK cells were found to home to lymph nodes where they killed allogeneic DCs in a perforin-dependent manner (174).

Interestingly, and consistent with their concomitant role during the early phase of immune responses, NK cells and DCs are often able to sense similar stimuli in parallel. It was reported by Moretta's group that TLR engagement not only activates immature DCs but also renders NK cells more prone to receive triggering signals from pathogen-associated molecules, thus exerting a regulatory control on the early steps of innate immune responses against infectious agents (16), as more specifically addressed in the next paragraph.

All these studies on DC/NK interactions indicate a critical role for NK cells in the initiation and regulation of immune responses and provide a strong rationale for a combined targeting of NK cells and DCs in novel immunotherapeutic strategies, harnessing this cellular cross-talk in the treatment of patients with cancer and chronic infections resistant to conventional therapies.

Alessandro Moretta's contribution to the knowledge on the molecular basis of these cellular interactions paved the way to clinical interventions exploiting DC/NK cell cooperation. As a matter of fact, NK cell activation by DCs is particularly efficient, since DCs promote both effector functions and survival/proliferation of NK cells (169). As a whole, these basic discoveries, largely achieved under Prof. Moretta's guidance, revealed a particular translational relevance. For instance, in the field of haplo-HSCT, a beneficial role of NK cells in mediating graft-vs.-leukemia effects and in preventing GvHD was highlighted. The support provided by DCs for the proliferation/survival of NK cells is relevant also for establishing more efficient protocols for *ex vivo* NK cell expansion, given that NK cell-based immunotherapies are currently being reconsidered in both post-transplant hematological settings and in immunotherapy strategies for advanced solid tumors (41, 119, 175–180).

Finally, DCs activated by NK cells are better inducers of the anti-tumor CTL response, at least *in vitro*, as compared with the standard mature DCs currently employed in DC-based clinical trials (181) and could therefore be considered in immunization strategies for the development of next-generation vaccines (182, 183).

Expression and Function of TLRs on Human NK Cells

Another field of research in which Prof. Moretta undoubtedly gave important contributions is the expression and function of TLRs in human NK cells. Indeed, in 2004 his group provided a solid experimental evidence that pathogen-associated products, known to strongly activate DCs and other innate immune cells, can also act on TLRs expressed by NK cells, inducing their activation both in terms of increased cytotoxicity and cytokine release (16). Alessandro Moretta and coworkers not only described the effect of TLR ligands on NK cell function, but also analyzed the role of TLR in the NK/DC crosstalk. This led to the concept of "NK cell-mediated editing of DCs," the "quality control" process by which NK cells select DCs that are suited for T cell priming. The capability of TLR agonists of potentiating NK cell function was further defined in subsequent studies (184–193). Thus, in 2010 a peculiar cooperation between TLR9 and KIR3DL2 in inducing triggering of NK cell function upon treatment with CpG-ODN (TLR9 ligand) was described (194, 195). This study revealed that KIR3DL2 can bind CpG-ODNs at the NK cell surface and shuttle them to endosomes

where TLR9 is localized, thus resulting in sharp down-regulation of KIR3DL2 surface expression and in TLR9-mediated induction of cytokine release. Moreover, it was demonstrated that the KIR Ig-domain involved in the direct recognition of CpG-ODN is represented by D0. Since this domain was hypothesized to be expressed by the putative ancestral mammalian KIR, these data suggested that, originally, certain KIRs could exert a function different from recognition of HLA class I molecules. Moreover, this newly defined functional capability of KIR3DL2 provided an important clue to understand the driving forces that led to the conservation of the KIR3DL2-encoding gene in all haplotypes, despite the low frequency, in the human population, of HLA-A*03 or -A*11 alleles (i.e., the ligands of KIR3DL2). Furthermore, in the Sézary Syndrome, in which KIR3DL2 represents a specific marker for the assessment of circulating tumor burden and for patient follow-up (76), CpG-ODN has been shown to promote not only the internalization of KIR3DL2 receptor but also the generation of apoptotic signals (196). Thus, CpG-ODN may exert a direct anti-tumor effect on Sézary cells through binding to KIR3DL2. In this context, a good clinical response without major side effects was observed upon class-B CpG-ODN subcutaneous administration in CTCL patients (197). CpG-DNA and other TLR agonists have been also explored as adjuvants for immunotherapy. Indeed, many clinical trials based on the use of CpG-ODNs as immunotherapeutic agents revealed that CpG-ODNs can promote Th1 immune responses and may be used in combination with chemotherapy to induce potent anti-tumor immune responses with relevant clinical benefits (186, 198, 199).

NK Cell Subsets in Anti-virus Responses

Besides cancer and other diseases, NCRs also contribute to the NK cell-mediated control of viral infections through the recognition of virus-infected cells. Indeed, the first characterized NCR-Ls were of viral origin, namely influenza virus hemagglutinins (200, 201). Later on, additional viral ligands were identified and, in most cases, they were shown to induce NK cell activation following NCR engagement (31, 78, 202). It is of note, however, that some viral NCR-Ls can inhibit NCR functions, representing a possible immune evasion strategy (203). It has been very recently demonstrated in mouse that NK cells may play a regulatory role during acute and

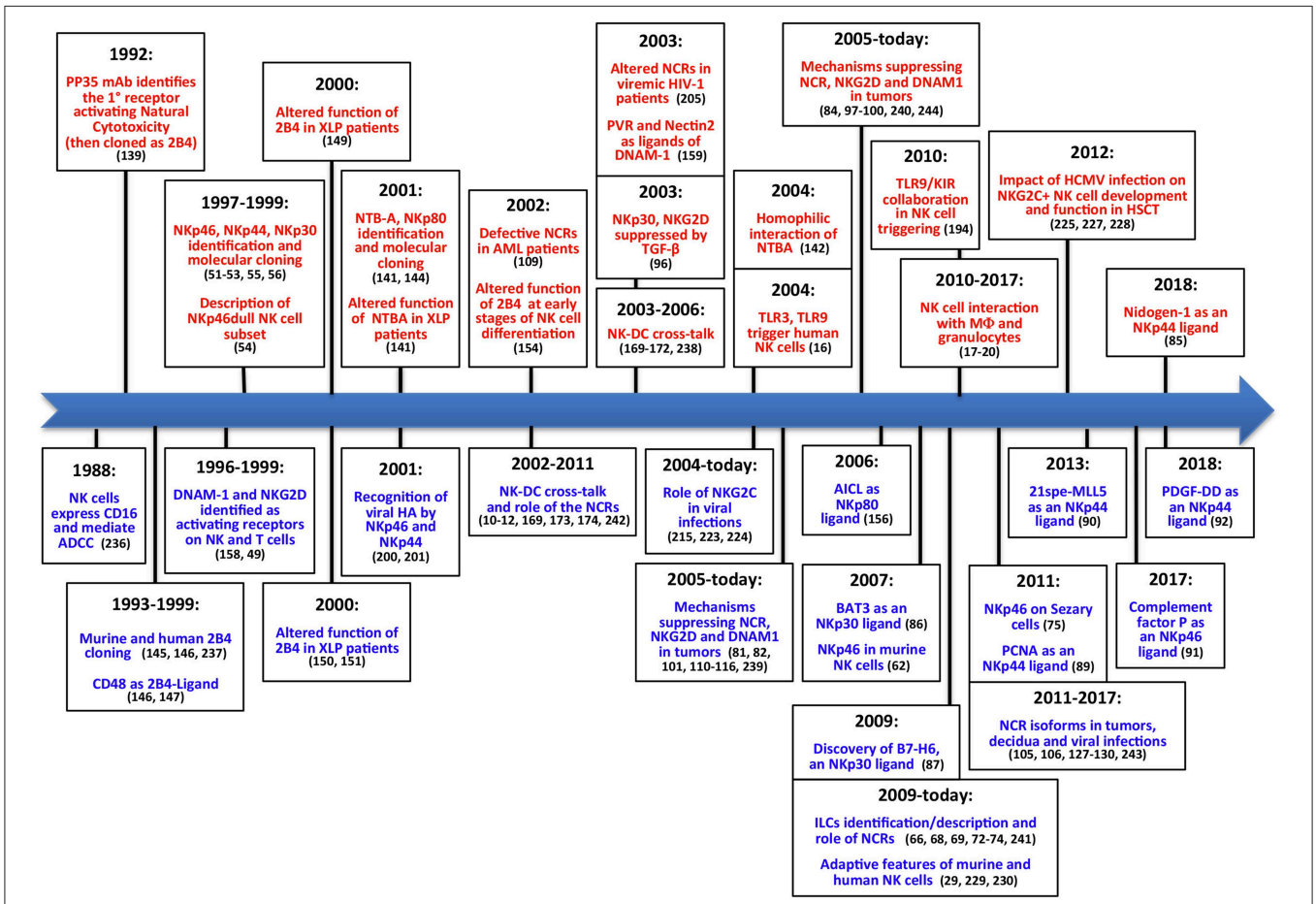

FIGURE 2 | The main steps concerning activating NK receptors/coreceptors. The timeline illustrates the main discoveries concerning NK cell activating receptors during a timespan of about 30 years. Contributions deriving from Alessandro Moretta's research group are indicated in red **(upper part)**, while contributions obtained by other groups are shown in blue **(lower part)**.

chronic lymphocytic choriomeningitis virus (LCMV) infection through the NKp46-mediated killing of LCMV-specific CD8 T cells (204).

In recent years Prof. Moretta and his co-workers gave major contributions to broaden our knowledge on NK cell diversity and functional specialization. This occurred primarily thanks to studies focused on NK cell-mediated responses to virus infections. Fundamental results came from the characterization of NK cells in patients chronically infected by HIV that revealed a deep functional impairment of NK cells likely determining their scarce capacity to efficiently control this virus. In this context, the relevance of NCR contribution to the course of HIV infection became clear when their reduced expression on NK cells in viraemic HIV-infected patients was demonstrated (205, 206). The NCR role in anti-viral response was also supported by the demonstration that NKp46 and NKp30 inducibility exerted a protective role in HIV-infected patients with excellent control not only of virus replication but, more importantly, also of retroviral reservoir (207, 208). Outside the HIV field, the study of NCR expression on NK cells similarly provided compelling evidence of their involvement in the response to acute HCV infection (209), and in HCV eradication in treated chronic carriers (210, 211). Interestingly, in chronically infected HIV patients the accumulation of a dysfunctional NK cell subset, virtually absent in healthy subjects, characterized by an aberrant $CD56^{neg}$ $CD16^{bright}$ surface signature (205, 212, 213) and defective DC editing was observed (214). This unusual population has been subsequently identified in several other pathological conditions including viral infections and immune deficiencies, in which these cells are responsible for an altered response to a chronic immune activation (215–219).

Besides HIV, a fundamental role in shaping NK cell repertoire and function has been described for CMV infection (220–222). Based on the pioneering studies by M. Lopez-Botet who first described the imprinting exerted by CMV on NK cells (223, 224), Alessandro Moretta contributed to identify CMV infection as a key driving force promoting the differentiation of functionally and phenotypically skewed NK cells with several studies conducted in HSCT recipients (225–228). In this setting, CMV infection/reactivation could induce not just NK cell maturation toward highly differentiated stages (characterized by the expression of CD94/NKG2C or activating KIRs), but also the unexpected acquisition of immunological memory. Indeed, NK cells maturing in CMV-reactivating patients share features with adaptive immune cells, such as long-term persistence, virus-induced clonal expansion, and epigenetic modifications (227, 229–234).

This anti-paradigmatic concept of memory or adaptive NK cells, to which Prof. Moretta contributed, holds important translational promise as this NK cell population characterized by longevity and superior ADCC ability, represents a potential tool for novel immunotherapeutic anti-cancer strategies, namely antibody-based tumor immunotherapies and generation of long-living anti-tumor CAR-NK cells (179, 235).

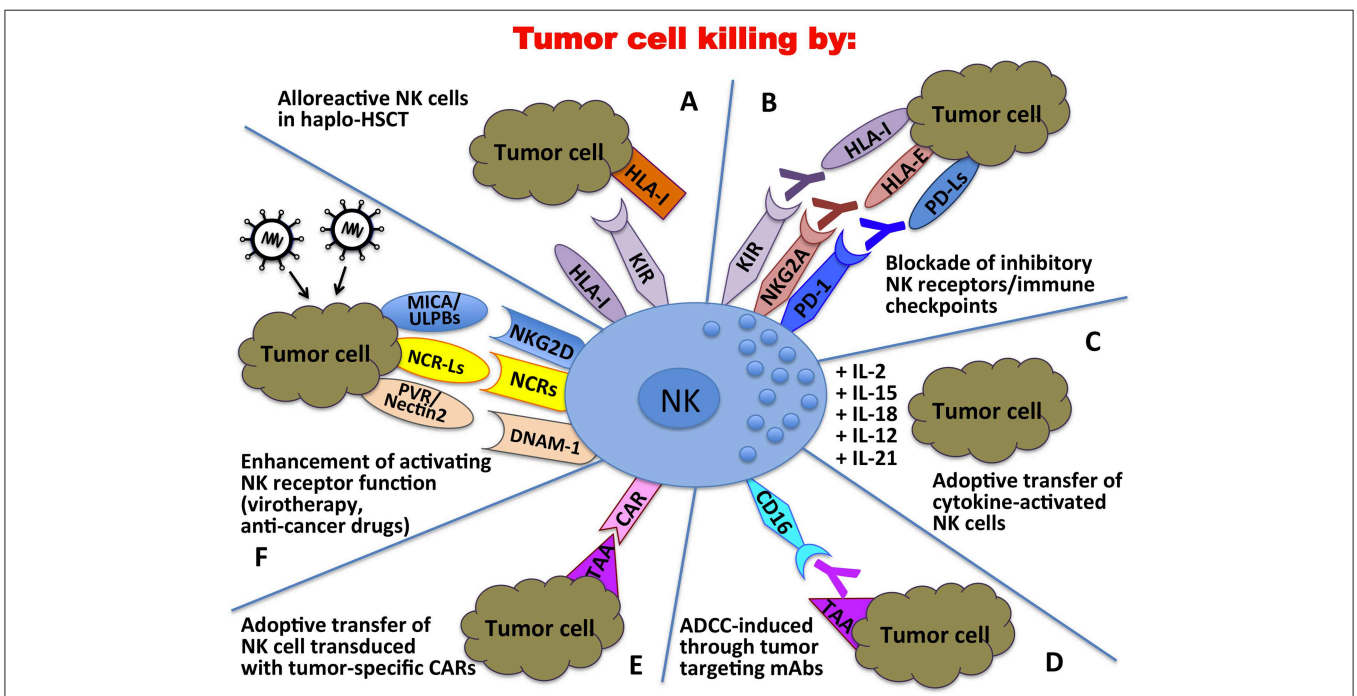

FIGURE 3 | Clinical applications of NK cells in the immunotherapy against tumors. In haplo-HSCT, alloreactive NK cells can kill residual leukemic cells **(A)**; mAbs directed against immune checkpoints can unleash/restore NK cell anti-tumor activity **(B)**; tumor cell killing can be enhanced by adoptive transfer of cytokine-activated NK cells **(C)** or NK cells transduced with tumor-specific Chimeric Antigen Receptors (CARs) **(E)**; tumor targeting mAbs can induce NK cell-mediated ADCC **(D)**; activating NK receptor function can be potentiated through oncolytic virotherapy or the use of anti-cancer drugs **(F)**.

NK CELL-BASED CLINICAL APPLICATIONS

Altogether, these discoveries in the field of NK cell biology (**Figure 2**) (236–243) paved the way to the exploitation of these cells in different anti-tumor therapeutic approaches (**Figure 3**). Over the years important achievements have been obtained, and promising novel strategies have been designed. The most advanced clinical application exploiting the NK cell anti-tumor potential is in the field of haplo-identical HSCT (40–42, 235), in which donor-derived alloreactive NK cells (i.e., unable to recognize recipient HLA class I molecules) can exert a potent anti-leukemia effect. Moreover, the adoptive transfer of NK cells, in an autologous or allogeneic setting, can be pursued following NK cell activation and expansion with cytokines (118–120). The blockade of HLA class I-specific inhibitory receptors using human/humanized mAbs can be used to enhance killing of HLA class I^{pos} tumor cells. These mAbs can be used in combination with mAbs interfering with the PD-1/PD-L axis, as PD-1 can be expressed by human NK cells (46, 244). Another clinical approach is represented by the induction of ADCC against tumor cells by the use of antibodies specific for tumor-associated antigens (119).

More recently, the CAR technology, originally designed for T lymphocytes, has been applied also to NK cells, with promising results in the therapy of both hematological and solid tumors (118, 120). The ever-growing knowledge of activating NK receptor/ligand interactions is being applied in several strategies aimed to potentiate triggering signals through virotherapy or by the use of anti-cancer drugs capable of enhancing the expression of activating ligands on tumor cells and activating receptors on NK cells (102, 117). In conclusion, NK cell-based therapy used in combination with conventional therapeutic protocols could become more and more a powerful tool to be used in the cure of cancer.

CONCLUDING REMARKS

By revisiting the discovery of the most important NK receptors and considering the technical approaches available at that time, one might have the impression that it has been simple to obtain those results. However, experienced researchers know that, actually, relevant pieces of information leading to a new discovery must be selected from an initially confusing, and often contradictory, mass of data. Alessandro had this ability, common to many gifted scientists, but he was also endowed with the uncommon talent of catching essential information and rendering simple what actually is very complex. We think that this has been the true and most important lesson for all of us and, undoubtedly, a major legacy for Immunology and Medicine.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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